

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PROPAMOCARB

SB 950-302, Tolerance #50308

November 19, 1986  
Revised August 26, 1988

I. DATA GAP STATUS

Combined (chronic & oncogenicity), rat: Data gap, inadequate study, no adverse effect indicated

Chronic rat: See Combined, Rat

Chronic dog: No data gap, possible adverse effect

Onco rat: See Combined, Rat

Onco mouse: Data gap, inadequate study, no adverse effect indicated

Repro rat: Data gap, inadequate study, no adverse effect indicated

Terato rat: No data gap, possible adverse effect

Terato rabbit: No data gap, no adverse effect

Gene mutation: No data gap, no adverse effect

Chromosome: No data gap, no adverse effect

DNA damage: No data gap, no adverse effect

Neurotox: Not required at this time

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**Note, Toxicology one-liners are attached**

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

File name T880826

Revised by M. Silva, August 26, 1988

## II. TOXICOLOGY SUMMARY

### COMBINED, RAT

018-019 & 013 058229-30 & 061589 "Previcur N (SN 66 752) Toxicity and Potential Tumorigenicity in Dietary Administration to Rats for 104 Weeks," (Schering Ag, 8/30/83). Previcur N (formulation with 76.1% technical propamocarb) was administered in diet to CD rats (50/sex/group) at 0, 40, 200 and 1000 ppm for 104 weeks. **No adverse effect indicated.** NOEL > 1000 ppm (no effects were observed in either sex at any dose level). **Not acceptable** (no MTD was reached and there was no justification for dose selection; high mortality in female control and 1000 ppm group). **Possibly upgradeable** (dose justification or a pilot study must be provided). An analysis of Previcur N (formulation) used in this study was provided in 013 061589. M. Silva, 8/11/88.

### CHRONIC RAT

See COMBINED, RAT above.

### CHRONIC DOG

**\*\* 014 & 013 058225 & 058223** "24-Month Oral (Feeding) Toxicity Study With Previcur N in Beagle Dogs," (Research & Consulting Company AG, 6/6/85). Previcur N (formulated material; propamocarb purity = 68 to 68.7%) was administered in diet to Beagle dogs (6/sex/group) at 0 (vehicle = water), 1000, 3000 and 10,000 ppm for 24 months. NOEL = 3000 ppm (males showed a significant decrease in mean corpuscular hemoglobin after 18 months and after 21 months showed a significant increase in platelets; thrombin time was significantly increased in males after 2 months; aspartate aminotransferase was significantly increased in males and calcium was significantly decreased after 4 months; females showed a significant decrease in reticulocytes after 12 months and a significant increase in mean corpuscular hemoglobin count after 3 months). **Possible adverse effect** (irreversible degeneration of the tapetum lucidum was observed in all dogs at 10,000 ppm). **Acceptable.** An analysis of Previcur N (formulation) was presented in 013 058223. M. Silva, 8/10/88.

### ONCOGENICITY, RAT

See COMBINED, RAT above.

### ONCOGENICITY, MOUSE

015-017 & 013 058226-8 & 061589 "Previcur N (SN 66 752) Potential Tumorigenicity to Mice in Dietary Administration for 104 Weeks," (Schering Ag, 8/30/83). Previcur N (formulated material containing 76.1% technical propamocarb) was administered in diet to CD-1 mice (60/sex/group) at 0, 20, 100 and 500 ppm (calculated as %technical propamocarb) for 104 weeks. **No adverse effect.** NOEL > 500 ppm (no effects were observed at any dose level in either sex). **Not acceptable** (an MTD was not reached in this study). **Possibly upgradeable** (CDFA must be provided with a pilot study or justification for dose selection). An analysis of Previcur N (formulation) was provided in 013 061589. M. Silva, 8/10/88.

## REPRODUCTION, RAT

010 043450 (4/25/83, Huntingdon) JAP, 11/86. Propamocarb (Previcur N), batch #271001, B CP 604, approximately 70%; fed in the diet at 0, 40, 200 or 1000 ppm, to 25/sex/group, for 100 days to P generation before mating for F1A litters; NOEL  $\geq$  1000 ppm; Unacceptable (no evidence MTD was reached, analysis of diet presented but not identified by date or week, parental animals not necropsied, clinical obs not included.) No adverse reproductive effect and marginal decrease in food consumption.

003 031162 One sentence summary of #043450 (Schering AG PF 62/81) JG 7/25/85

## TERATOLOGY, RAT

**\*\* 013, 009 061590, 043438** "Previcur N (CP 604) Embryotoxicity Including Teratogenicity Study in Rats After Daily Intragastric Administration From Day 6 to Day 19 of gestation - TX 80.348; Report PF 62/81," (Schering AG, 11/2/81). Previcur N (formulation = 68% technical propamocarb; Code # ZK 66.752; batch #3005100 - CP 604) was administered by gavage to mated Wistar rats (25/group) at 0 (vehicle = water), 0.1, 0.3, 1.0 and 3.0 ml/kg from day 6-19 of gestation (day 0 = day vaginal plug or vaginal sperm detected). Maternal NOEL = 1.0 ml/kg (mortality, increased incidence of clinical signs and decreased weight gain in dams at 3.0 ml/kg). **Possible adverse effect.** Developmental NOEL = 0.3 ml/kg (increased % of fetuses with minor skeletal changes). Initially reviewed as unacceptable (J. Parker, 10/20/86), the status was changed to **acceptable** upon receipt of the requested analysis of dosing solutions (013 061590). M. Silva, 8/16/88.

## TERATOLOGY, RABBIT

010 043448 (Schering, 2/16/81) JAP, 10/28/86; Previcur N, Code # SN66 752, batch #271001B CP 604, approximately 70% purity; tested at 0, 0.2, 0.4 or 0.8 ml/kg, by oral gavage, days 6-18 of gestation to 15-20 NZW rabbits/group; maternal NOEL = 0.2 ml/kg (body weight loss, abortion and death); developmental NOEL = 0.2 ml/kg (resorptions and decreased fetal weight). Unacceptable, not upgradeable

010, 013 043449, 061587-8 "Previcur N (CP 604) - Embryotoxicity Including Teratogenicity Study in Rabbits After Daily Intragastrical Administration From Day 6 to Day 18 of Gestation," (Schering Ag, 1/9/81). Previcur N (formulation in aqueous solution; technical = 95.1%; code#: ZK 66.752; batch #271001 CP 604, 69.4% technical in formulation) was administered by gavage to mated New Zealand White rabbits (18-20/group) at 0 vehicle = water, 0.02, 0.06, 0.2, 0.4 or 0.8 ml/kg during days 6-18 of gestation (day 0 = confirmed vaginal smear). Maternal NOEL = 0.2 ml/kg (decreased body weight gain at 0.4 and 0.8 ml/kg). Developmental NOEL = 0.2 ml/kg (significantly decreased post-implantation loss). **Unacceptable** (not all fetuses examined visceraally and skeletally as required by current FIFRA guidelines). **Not upgradeable.** J. Parker, 10/28/86. Subsequent information was submitted by Nor-Am Chemical Company: 013 061587 contained an analysis of dosing solutions and 013 061588 contained individual clinical data. This information was acceptable, however the study is still **not acceptable and not upgradeable** since all fetuses were not examined. M. Silva, 8/16/88.

003 31163 One-sentence summary of #043449 (E.P.A. Acc. No. 245108) JG 7/25/85

008 22103 One-sentence summary of #043449

**SUMMARY:** While neither of these studies complies fully with FIFRA guidelines, due to the number

of dose levels evaluated in both studies, there are sufficient data available to adequately assess the potential toxicity of Previcur N. The registrant has supplied the additional data requested and it is acceptable, therefore these studies together fill the data gap for rabbit teratology.

#### MUTAGENICITY, GNMU

003/008 031159 One sentence summary of Ames test EPA ACC. # 237432. Maximum concentration of 2.5 ul,  $\pm$  S9. Full study not on file with CDFA. JG, 7/25/85.

009 043439 Salmonella (8/77, Inveresk) JG, 11/18/86. Propamocarb, SN 66.752 (ZK.66.752) - CP 604, batch no. 270201 B00000, 70% purity; tested at 0, 3.5, 17.5, 87.5, 350 or 1750 ug/plate, in triplicate, 1 trial, strains TA1535, TA1537, TA1538, TA98 and TA100  $\pm$  S9 from rat liver; no evidence of cytotoxicity or mutation; Unacceptable, not upgradeable. No individual plate counts, no dose justification, and no repeat trial.

009 043443 Saccharomyces (5/27/80, Litton) JG, 11/19/86. Previcur N, Batch no. 271001B00000, no purity stated, tested at 1000, 2500, 5000 or 10,000 ug/plate in triplicate, 1 trial, with strains S138 and S211c,  $\pm$  S9 from rat liver; no toxicity or mutation; Unacceptable, not upgradeable. No purity stated or repeat trial.

009 043445 Saccharomyces (10/85, Litton) JG, 11/18/86. Previcur N, Batch no. 320072-75, no purity stated, tested at 1.0 to 25.0 ul/ml incubated overnight in liquid culture; strains S138 and S211a; with rat liver S9 activation, in quadruplicate, no increase in # revertants or reversion frequencies; Unacceptable. No purity statement, or individual plate counts.

013 061585 Appendix 3 contains an analysis of Previcur N (formulation) batch no. 271001 S 00000 used in 043442-4. M. Silva, 8/15/88.

013 061586 This submission contains a duplicate copy of the protocol and methods for "Reverse Mutation Induction in Saccharomyces Cerevisiae Strains S138 and S211" originally found in 043443.

**SUMMARY:** Although none of the above studies complies fully with Gene-Tox guidelines, taken together there are sufficient data available to assess the mutagenicity of propamocarb in microbial systems. In addition, 043445 is, in essence, a repeat trial for 043443 in Saccharomyces. The registrant has submitted the requested data (analysis of test material 013 061585) to CDFA and therefore, these studies together fill the data gap for gene mutation.

#### MUTAGENICITY, CHROMOSOME

\*\* 009 & 013 043440, 061583 & 061585 "Micronucleus Test on CP 604 (SN 66752, Previcur N)," (Schering Ag, 1/22/80). Previcur N (formulation containing 76.1% propamocarb) was administered by gavage to CFLP mice (5/sex/group) in 2 equal dosages, separated by an interval of 24 hours at 0 (vehicle = 1% methylcellulose), 1250, 2500 and 5000 mg/kg. The mice were killed 6 hours after the 2nd dose. In a second test, 5 mice/sex/group were tested at 0 and 2500 mg/kg and the mice were killed at 12, 24, 36 and 48 hours after the 2nd dose. **No adverse effect indicated.** No significant chromosome damage was observed in either test. Positive controls functioned as expected. This study was previously reviewed as unacceptable by J. Gee, 11/18/86 (No purity statement, single sampling time at 6 hours) but was upgraded to **acceptable** upon receipt and review of the entire study (013 061583) at CDFA. An analysis of Previcur N (formulated) was in 013 061585. M. Silva, 8/12/88.

003 031160 One sentence summary of # 43440 below. JG 7/25/85

003 031161 One sentence summary of #43441 below. JG, 7/25/85.

009 043441 Mouse, Dominant Lethal. (11/79, SRI) JG, 11/18/86. Previcur N, Code #SN 66 752, batch #27 1001 B, Recipe No. CP 604), 69.2% purity, tested at 0, 500, 1000, 2000, 4000 or 8000 ppm in drinking water for 8 weeks to 20 ICR/SIM mice/group; dose-related decreases in water consumption and body weights, and no dominant lethal effects observed; Unacceptable, upgradeable. No analyses of drinking solutions.

#### MUTATION, DNA

009 043442 & 043444 Saccharomyces (5/27/80, Litton) JG, 11/19/86. Previcur N, Batch no. 271001B00000, no purity stated, tested at 1000, 2500, 5000 or 10,000 ug/plate in triplicate, 1 trial, strains D<sub>4</sub> and D<sub>5</sub>,  $\pm$  S9 from rat liver; no toxicity or mutation; Unacceptable, not upgradeable. No purity stated or repeat trial.

013, 009 058224, 043446 "Gene Conversion and Reverse Mutation Induction Assays With Saccharomyces cerevisiae D4, S138 and S211c," (Litton Bionetics, 10/85). Previcur N (formulation = 68.9% propamocarb technical; batch no. 320072-75) was tested on D4 with rat liver activation at 10.0, 12.5, 15.0, 20.0 and 25.0 ul/ml. Liquid cultures were incubated overnight, then plated. No genetic conversions were induced. **Unacceptable** (no purity statement or individual plate counts). J. Gee, 11/18/86. The requested information (purity of test article and individual plate counts) was received at CDFA, reviewed and found acceptable (013 058224). The status of this study remains **unacceptable** and **not upgradeable** since no tests were run without activation. M. Silva, 8/17/88.

**SUMMARY:** As stated under MUTAGENICITY, GNMU, while neither study fully complies with guidelines, taken together they fill the data gap (record# 043446 is a partial repeat of 043442, -44). The registrant has submitted the requested data and they are acceptable (013 058224).

#### NEUROTOXICITY

Not required at this time.